ISSN 0216-3438 (Print). ISSN 2621-1122 (Online)
Jurnal Profesi Medika : Jurnal Kedokteran dan Kesehatan

THE ASSOCIATION BETWEEN PATIENT CHARACTERISTICS AND DISEASE OUTCOMES OF COVID-19 IN JEMBER, INDONESIA

Diana Chusna Mufida[1], Putu Ayu Laksmi Lestari[2], Azham Purwandhono[3] , Enny Suswati[1], Angga Mardro Raharjo[4]

[1]Department of Microbiology, Faculty of Medicine, University of Jember, Jember, 68121 Indonesia
[2] Faculty of Medicine, University of Jember, Jember, 68121 Indonesia
[3] Department of Anatomical Pathology, Faculty of Medicine, University of Jember, Jember, 68121 Indonesia
[4] Department of Public Health, Faculty of Medicine, University of Jember, Jember, 68121 Indonesia

*Correspondence email: chusna.fk@unej.ac.id

ABSTRACT

COVID-19 can cause serious conditions in both comorbid and elderly patients; hence, they need to be given proper follow-up treatment. This study aimed to determine the association between patient characteristics and disease outcomes of COVID-19 in Jember, Indonesia. This research is an analytic observational study with a cross-sectional approach. The sample was 304 patients confirmed positive for COVID-19 at the COVID-19 referral hospitals in Jember. This study used medical record data analyzed using both univariate and bivariate tests. Patient characteristics related to the disease outcomes in patients who were positive for COVID-19 in Jember, are as follows: age (p = 0.000), clinical symptoms (p = 0.017), comorbidities (p = 0.000), and complications (p = 0.000). The unrelated variables were sex (p = 0.455), education level (p = 1.000), domicile (p = 1.000), occupation (p = 0.322), and smoking history (p = 0.147). Patients most at risk of developing fatal outcomes are those with complications. Patient characteristics associated with the disease outcomes in patients positive for COVID-19 were age, clinical symptoms, comorbidities, and complications. While, those that were not related to the disease outcomes in patients were sex, education level, occupation, domicile, and smoking history.

Keywords: COVID-19; Disease outcome; Patient characteristics

INTRODUCTION

COVID-19 is a new disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. The pathogen that causes COVID-19 is the Betacoronavirus which belongs to the Sarbecovirus subgenus. In December 2019, at Wuhan City, Hubei Province, China, this disease appeared for the first time with the discovery of cases of respiratory disease with distinctive findings on radiological images.[1]

On March 11, 2020, WHO declared that the COVID-19 outbreak became a global pandemic.[2] One study suggested that male patients and those with anorexia may have worsening disease progression.[3] Older patients (> 65 years) with comorbidity and ARDS have a high risk of death.[4] COVID-19 patients from the older age groups have much more severe disease and have a worse response to treatment than younger age groups[5]. Men with COVID-19 infection have > 50% higher risk of severe infection and death than women[6]**.** Symptoms of fever are most common in patients and strongly associated with the patient's clinical status[7], besides that smokers are susceptible to respiratory viruses.[8]

This global pandemic has affected all levels of society, both in villages and cities. Health staff, social workers, and educators have a higher risk of severe SARS-CoV-2 infection.[9] The government has made much effort. Almost the entire area of Jember regency was currently categorized into an orange zone with a medium risk level based

DOI : http://dx.doi.org/10.33533/jpm.v15i0.3441

on data published by the Provincial Government of East Java.[10] COVID-19 cases in Jember were increasing, with 620 positive cases as of September 9, 2020, 513 recovered cases, and 43 deaths. The Case Fatality Rate (CFR) was 6.94%.[11] There is still no definite vaccine and drug to deal with COVID-19 cases, while the spread of COVID-19 is significantly high even though the mortality rate is low. COVID-19 can cause severe conditions in elderly patients and those with comorbidity**;** therefore, it is essential to know the association between the characteristics of a positive patient with COVID-19 and the disease outcomes so that the patient can be diagnosed be provided with proper management.

MATERIAL AND METHODS

Study design and participants

This study was an observational analytic with a cross-sectional approach. This was conducted at three COVID-19 referral hospitals in Jember, namely Kaliwates Hospital, Jember Klinik Hospital, and Citra Husada Hospital, from August 2020 to February 2021. The population of this study was all patients who tested positive for COVID-19 at those COVID-19 Referral Hospitals from April to November 2020. The sampling technique used was total sampling with a number of samples of 304. This study utilized the patients' medical records as the instrument. The independent variables of this study were age, sex, level of education, occupation, domicile, clinical symptoms, history of comorbidity, history of smoking, and complications. In contrast, the dependent variable was the patient's disease outcomes. This study has received ethical approval from the Ethics Commission of the Faculty of Medicine, University of Jember.

Procedures

This research began with population determination, namely, patients tested positive for COVID-19 at the Referral Hospitals for COVID-19 in Jember. Sample collection was conducted by using a total sampling technique with the following inclusion criteria: patients tested positive for COVID-19 with evidence of positive RT-PCR swabs and or Fast Molecular Test (TCM) and the exclusion criteria as follows: patients who were tested positive for COVID-19 with medical record data that did not meet the requirements set by the researchers. The medical record data was declared eligible if it contains at least 5 of the nine patient characteristics determined by the researchers. After collecting the sample, the patient's characteristics were recorded and grouped according to the disease outcome of the patients who tested positive for COVID-19 based on the medical record data.

Statistical analysis

This study utilized univariate and bivariate analyses. Univariate analysis was performed by calculating the distribution and percentage of each variable. Bivariate analysis was carried out to determine the association between age, sex, education level, occupation, domicile, clinical symptoms, comorbidity history, smoking history, and complications with patient's disease outcome who were tested positive for COVID-19 in Jember. The Chi-Square Test was the main statistical test with a $p < 0.05$ or 95% confidence level. If the Chi-Square Test requirements were not fulfilled, then the alternative test applied was the Fisher's Exact Test

RESULT

Sociodemographic and clinical characteristics of patients who tested positive for COVID-19 are shown in Table 1. Patients who tested positive for COVID-19 in Jember were mostly aged ≥ 45 years, with a total of 154 (50.7%) patients of different types. Male patients of 156 patients (51.3%). 245 (80.6%) patients had met the 9-year compulsory education level. Two hundred thirty-one patients were indoor workers (76%), and the majority of the patients lived in cities with as many as 189 (62.2%) patients. A total of 257 (84.5%) patients had clinical symptoms. A total of 272 (89.5%) patients had no smoking history, and 32 (10.5%) patients had a

smoking history. A total of 105 (34.5%) patients had comorbidity. A total of 40 (13.2%) patients had complications. Disease outcomes in patients confirmed positive for COVID-19 in Jember are as follows: 270 (88.8%) patients recovered, and 34 (11.2%) patients died.

Table 1. Sociodemographic and clinical characteristics of patients confirmed positive for COVID-19

Characteristics	Total (N)	Percentage (%)
Age		
< 45 Years	150	49.3
≥ 45 Years	154	50.7
Sex		
Male	156	51.3
Female	148	48.7
Level of education		
Finished the 9-year compulsory education	245	80.6
Unfinished the 9-year compulsory education	59	19.4
Occupation		
Indoor	231	76
Outdoor	73	24
Domicile		
City	189	62.2
Village	115	37.8
Clinical symptoms		
Have clinical symptoms	257	84.5
Have no clinical symptoms	47	15.5
Comorbidity history		
With comorbidity	105	34.5
Without comorbidity	199	65.5
Smoking history		
Smoking	32	10.5
Not Smoking	272	89.5
Complications		
With complication	40	13.2
Without complication	264	86
Disease outcome		
Death	34	11.2
Recovery	270	88.8

The clinical symptoms, comorbidity, and complications were experienced by patients who tested positive for COVID-19 in this study. The most frequently occurring clinical symptom was cough in 167 (54.9%) patients, and the least frequently occurring was chest pain in 6 (2%) patients. The most common comorbidity among the patients was hypertension - cardiovascular disease in 46 (15.1%) patients, and the least common was COPD in 1 (0.3%) patients. The most frequent complication experienced by patients was ARDS in 25 (8.22%) patients (Table 2).

The association between patient characteristics and disease outcomes in patients tested positive for COVID-19 in Jember, as follows: age (p-value = 0.000), clinical symptoms (p-value = 0.017), history of comorbidity (p-value = 0.000), and complications (p-value = 0.000). Meanwhile, the unrelated variables were sex (p = 0.455), education level (p = 1.000), domicile (p = 1.000), occupation (p = 0.322), and smoking history (p = 0.147). Patients aged≥ 45 years had a greater risk of 7.142 to experience a fatal outcome than those aged <45 years. Patients with clinical symptoms were 14.664 times more likely to experience a fatal outcome than those who did not have clinical symptoms. Patients with a history of comorbidity had a 9.495 times greater risk of experiencing a fatal outcome than those who did not have comorbidity. Patients with complications had a 25.667 times greater risk of experiencing a fatal outcome than those without complications (Table 3).

Table 2 Clinical symptoms, comorbidities, and complications experienced by patients confirmed positive for COVID-19

Patient characteristic	Total (N)	Percentage (%)
Clinical symptoms		
Asymptomatic	47	15.5
Fever	116	38.2
Cough	167	54.9
Headache	35	11.5
Abdominal pain	43	14.1
Nausea vomiting	64	21
Shortness of breath	101	33.2
Chest pain	6	2
Weak limb-stroke	27	8.9
Kidney disorders	-	-
Others	10	3.28
Comorbidity		
Without comorbidity	199	65.5
Diabetes mellitus	41	13.5
Hypertension – Cardiovascular Disease	46	15.1
Asthma	11	3.6
COPD	1	0.3
TBC	2	0.6
Obesity	0	
Stroke	2	0.6
Malignancy	2	0.6
Pregnancy	4	1.3
Other	12	4
Complications		
Without complication	264	86.84
ARDS	25	8.22
Dyspnea	8	2.63
Sepsis	5	1.64
Cardiac arrest	2	0.65
Others	1	0.33

Table 3. Association between patient characteristics and disease outcomes of patients confirmed positive for COVID-19

Characteristics	*Disease outcomes of COVID-19 positive patients in Jember*				*P-Value*	*OR*
	Deaths		**Recovery**			
	n	**%**	**n**	**%**		
Age						
≥ 45 Years	29	85.3	121	44.8	0.000	7.142
< 45 Years	5	14.7	149	55.2		
Sex						
Male	20	58,8	136	50.4	0.455	
Female	14	41.2	134	49.6		
Level of education						
Finished the 9th year compulsory education	27	79.4	218	80.7	1.000	
Unfinished the 9th year compulsory education	7	20.6	52	19.3		
Occupation						
Indoor	26	76.5	205	75.9	1.000	
Outdoor	8	23.5	65	24.1		
Domicile						
City	18	52.8	171	63.3	0.322	
Village	16	47.1	99	36.7		
Clinical symptoms						
With clinical symptoms	34	100	223	82.6	0.017	14.664
Without clinical symptoms	0	0	47	17.4		
Smoking history						
Smoking	6	17.6	26	9.6	0.147	
Not Smoking	28	82.4	244	90.4		
Comorbidity history						
With comorbidity	27	79.4	78	28.9	0.000	9.495
Without comorbidity	7	20.6	192	71.1		
Complications						
With complication	22	64.7	18	6.7	0.000	25.667
Without complication	12	35.3	252	93.3		

DISCUSSION

The Association between age and disease outcome

The age group ≥ 45 years had the highest percentage of deaths, namely 85.3%. The results of this study are in line with a study proposing that old age is the strongest risk factor associated with fatal disease outcomes.[12] COVID-19 patients aged ≥50 years had a 15.4-fold higher risk of death than those aged <50 years. Increased mortality in elderly patients is due to decreased immune function.[13] The induction of pro-inflammatory cytokines after infection is not sufficiently controlled by anti-inflammatory mechanisms in the elderly so that it has the potential to cause a poor prognosis.[14]

Association between sex and disease outcome

The percentage of male patients who died was 58.8%, while women were 41.2%. This suggests that there was no association between sex and hospital mortality in COVD-19 patients because the mechanisms underlying sex were not strong enough to significantly influence hospital mortality due to a complex variety of causes.[15]

The Association between education level and disease outcome

The Chi-Square Test results prove that there is no association between education level and disease outcome in patients who were tested positive for COVID-19 in Jember. Previous research related to this has yet to be found. The level of education with the outcomes of the disease in patients was not significantly related because the disease outcome was related to the patient's condition and the severity of the disease and closely related to the treatment undertaken during hospitalization.

The Association between occupation and disease outcome

Chi-Square Test result proves no association between occupation and disease outcomes in patients who were tested positive for COVID-19 in Jember. The absence of an association between occupation and disease outcomes in patients may be due to differences in patient immunity when infected with COVID-19 and differences in their medical history. This study shows that more patients infected with COVID-19 work indoors than outdoors. This may be caused by environmental influences and the person's immunity. Patients who work in indoor areas, such as office workers, tend to work in closed areas, have low exposure to direct sunlight, and sometimes have less supportive air circulation.

Meanwhile, for patients who work in outdoor areas, such as farmers – the majority occupation in Jember, it is possible to get sufficient sun exposure and good air circulation. This may provide benefits to strengthen the immune system. Sun exposure can trigger the formation of vitamin D naturally, which plays a role in supporting increased body immunity. Vitamin D has a direct antiviral effect, especially against coronavirus. Vitamin D can modulate and regulate the immune and oxidative responses to COVID-19 infection[16].

The association between domicile and disease outcome

Based on the results of this study, it was found that there was no significant difference between the number of patient deaths due to COVID-19 in villages and cities. This may be caused by the fact that more rural residents did not follow the strict measure of COVID-19 prevention behaviour than urban residents[17]. This study also shows that more patients infected with COVID-19 live in cities than in villages. One of the factors that cause the spread of COVID-19 is population density. Cities are places with a high population density. This allows the level of interaction between residents to be higher, causing any infectious disease to spread rapidly.[18]

The association between clinical symptoms and disease outcome

The Chi-Square Test results prove that there is an association between clinical

symptoms and disease outcomes in patients who are tested positive for COVID-19 in Jember. The clinical symptoms most frequently experienced by patients were cough (54.9%), fever (38.2%), and shortness of breath (33.2%). Patients with clinical symptoms were more likely to experience a fatal outcome than those who did not. Several factors are associated with the worsening clinical status in adults with COVID-19: fever, cough, and dyspnea.[7]

The association between history of smoking and disease outcome

Fisher's Exact Test results prove no association between smoking history and disease outcomes in patients who tested positive for COVID-19 in Jember. 6 (17.6%) patients with a history of smoking died. This study contradicts a study that stated that smoking status was associated with the severity of disease and mortality in COVID-19 patients[19].

The association between comorbidity and disease outcome

Patients with comorbidity have the highest mortality percentage at 27 (79.4%). Comorbidity most commonly found in patients were hypertension - a cardiovascular disease with as many as 46 (15.1%) patients, 41 (13.5%) diabetes mellitus patients and 11 (3.6%) asthma patients. Patients with more than one comorbidity are strongly associated with poor disease outcomes. This proves that the comorbidity history of more than one patient contributes to the complexity of the disease and often causes patients to have poor outcomes.[20] The common comorbidity experienced by the COVID-19 patients were hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease and chronic kidney disease.[8] ACE2 receptor expression is increased in several comorbid conditions such as hypertension and diabetes. SARS-CoV-2 attacks cells via the ACE2 receptor. Therefore, a history of comorbidity increases the severity of COVID-19 cases.[21]

The association between complications and disease outcome

Patients with complications had a greater percentage (64.7%) of death than those without complications. Complications that often occurred in patients in this study were ARDS (acute respiratory distress syndrome) in 25 (8.22%) patients, dyspnea in 8 (2.63%) patients, and sepsis in 5 (1.64%) patients. ARDS was the most frequent complication of patients in this study. ARDS is a condition associated with various disease processes resulting in decreased lung growth and severe hypoxemia. Cytokine storms are one of the main features of ARDS in COVID-19 patients. Pathological evidence of ARDS COVID-19 cases shows clear desquamation of pneumocytes, formation of hyaline membranes, and pulmonary edema.[22] Sepsis is a life-threatening organ dysfunction caused by dysregulation of the immune system against infection.[23] The pathophysiology of sepsis is related to an immune response initiated by pathogens that attack the host. Then the immune system fails to return to a homeostatic state, culminating in a pathological syndrome characterized by continued excessive inflammation and suppressed immunity.[24] COVID-19 patients who suffer from sepsis show changes such as those found in septic shock, including changes in mental condition, dyspnea, reduced urine output, faster heart rate, weak pulse, and cold extremities.[25] Dyspnea was statistically and significantly higher in the critical or deceased group.[26] Dyspnea indicates poor lung function and a lack of oxygen. Therefore, COVID-19 patients with dyspnea may be more likely to develop the severe and critical disease.[27]

Limitations

There are several limitations in implementing this research, including using medical record data as the data source. There may be incompleteness in implementing medical record data, which prevents the researchers from getting many more samples. This study used a cross-sectional approach; hence, it has not explained the course of the

disease in detail. In this study, not all patient characteristics related to disease outcomes were studied, so further research needs to be carried out in this regard.

CONCLUSION

Most of the patients who tested positive for COVID-19 in Jember aged ≥ 45 years were male. Patients were dominantly indoor workers, and the majority lived in cities. Patients who were most at risk of experiencing the outcome of death were patients who experienced complications. Patient characteristics related to the disease outcomes in patients who tested positive for COVID-19 in Jember were age, clinical symptoms, comorbidity history, and complications. Meanwhile, patients' unrelated disease outcomes were sex, education level, occupation, domicile, and smoking history. Related institutions are advised to be more careful in handling patients who are elderly, have a comorbidity, and experience complications to avoid more severe disease and death rates. People with advanced age and a history of comorbidity are always expected to be aware of the condition if they experience illness. Therefore, if they feel the symptoms of COVID-19, they are advised to examine the nearest health facility.

REFERENCES

1. Wang, Z., Yang, B., Li, Q., Wen, L., Zhang, R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*. 2020. *71*(15), 769–777. https://doi.org/10.1093/cid/ciaa272
2. WHO. 2020. Virtual press conference on COVID-19 – 11 March 2020. https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio emergencies-coronavirus-press-conference-full-and-final 11mar2020.pdf?sfvrsn=cb432bb3_2. Accessed September 9, 2020.
3. Mo, P., Xing, Y., Xiao, Y., Deng, L., Zhao, Q., Wang, H., et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*. 2020. https://doi.org/10.1093/cid/ciaa270
4. Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*. 2020.*8*(5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5
5. Liu, Y., Mao, B., Liang, S., Yang, J. W., Lu, H. W., Chai, Y. H., et al. Association between age and clinical characteristics and outcomes of COVID-19. In *European Respiratory Journal*. 2020.https://doi.org/10.1183/13993003.01112-2020
6. Kragholm, K., Andersen, M. P., Gerds, T. A., Butt, J. H., Østergaard, L., Polcwiartek, C., et al. Association Between Male Sex and Outcomes of Coronavirus Disease 2019 (COVID-19)—A Danish Nationwide, Register-based Study. *Clinical Infectious Diseases*. 2020. https://doi.org/10.1093/cid/ciaa924
7. do Nascimento, I. J. B., von Groote, T. C., O'Mathúna, D. P., Abdulazeem, H. M., Henderson, C., Jayarajah, U., et al. Clinical, laboratory and radiological characteristics and outcomes of novel coronavirus (SARS-CoV-2) infection in humans: A systematic review and series of meta-analyses. *PLoS ONE*. 2020 https://doi.org/10.1371/journal.pone.0239235
8. Brake, S. J., Barnsley, K., Lu, W., McAlinden, K. D., Eapen, M. S., Sohal, S. S. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). *Journal of Clinical Medicine*. 2020. https://doi.org/10.3390/jcm9030841
9. Mutambudzi, M., Niedzwiedz, C. L.,

Macdonald, E. B., Leyland, A. H., Mair, F. S., Anderson, J. J., Morales, C. A. C., Cleland, J., Forbes, J., Gill, J. M., Hastie, C., Ho, F. K., Jani, B. D., Mackay, D. F., Nicholl, B. I., O'Donnell, C. A., Sattar, N. I., Welsh, P. I., Pell, J. P., … Demou, E. Occupation and risk of COVID-19: prospective cohort study of 120. *SSRN Electronic Journal*. 2020. 1–24.

10. East Java Provincial Government. 2020. Map of the Distribution of COVID-19 in East Java. http://infocovid19.jatimprov.go.id/. Accessed September 10, 2020.
11. Jember Regency Government. COVID-19 Case in Jember Regency. http://www.jemberkab.go.id/. 2020. Accessed September 9, 2020.
12. Chen, R., Liang, W., Jiang, M., Guan, W., Zhan, C., Wang, T., et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. 2020. *Chest*, *158*(1), 97–105. https://doi.org/10.1016/j.chest.2020.04.010
13. Biswas, M., Rahaman, S., Biswas, T. K., Haque, Z., Ibrahim, B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. In *Intervirology*. 2020 .https://doi.org/10.1159/000512592
14. Qian, S. Z., Hong, W. D., Lingjie-mao, Chenfeng-lin, Zhendong-fang, Pan, J. Y. Clinical Characteristics and Outcomes of Severe and Critical Patients With 2019 Novel Coronavirus Disease (COVID-19) in Wenzhou: A Retrospective Study. *Frontiers in Medicine*. 2020. *7*(September), 1–7. https://doi.org/10.3389/fmed.2020.552002
15. Liu, J., Zhang, L., Chen, Y., Wu, Z., Dong, X., Teboul, J. L., et al. association of sex with clinical outcomes in COVID-19 patients: A retrospective analysis of 1190 cases. *Respiratory Medicine*. 2020.https://doi.org/10.1016/j.rmed.2020.106159
16. Yisak, H., Ewunetei, A., Kefale, B., Mamuye, M., Teshome, F., Ambaw, B., et al. Effects of vitamin d on covid-19 infection and prognosis: A systematic review. In *Risk Management and Healthcare Policy*. 2021. https://doi.org/10.2147/RMHP.S291584
17. Chen, X., Chen, H. H. Differences in preventive behaviors of covid-19 between urban and rural residents: Lessons learned from a cross-sectional study in china. *International Journal of Environmental Research and Public Health*. 2020 https://doi.org/10.3390/ijerph17124437
18. Bhadra, A., Mukherjee, A., Sarkar, K. Impact of population density on Covid-19 infected and mortality rate in India. *Modeling Earth Systems and Environment*. 2021 https://doi.org/10.1007/s40808-020-00984-7
19. Listyoko, A. S., S. Djajalaksana, dan T. Astuti. Association between smoking and the severity and mortality of Covid-19 patients hospitalized at RS Saiful Anwar Malang. *Medica Hospitalia : Journal of Clinical Medicine*.2020. https://doi.org/10.36408/mhjcm.v7i1A.464
20. Giannouchos, T. V., Sussman, R. A., Mier, J. M., Poulas, K., Farsalinos, K. Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases. *European Respiratory Journal*. 2020. https://doi.org/10.1183/13993003.02144-2020
21. Landi, F., Barillaro, C., Bellieni, A., Brandi, V., Carfì, A., D'Angelo, M., et al. The New Challenge of Geriatrics: Saving Frail Older People from the SARS-COV-2 Pandemic Infection,. *Journal of Nutrition, Health and Aging*. 2020. https://doi.org/10.1007/s12603-020-1356-x
22. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., et al. Pathological

findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine*. 2020. https://doi.org/10.1016/S2213-2600(20)30076-X

23. Singer, M., Deutschman, C. S., Seymour, C., Shankar-Hari, M., Annane, D., Bauer, M., et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). In *JAMA - Journal of the American Medical Association*.2016. https://doi.org/10.1001/jama.2016.0287
24. Gu, X., Zhou, F., Wang, Y., Fan, G., Cao, B. Respiratory viral sepsis: Epidemiology, pathophysiology, diagnosis and treatment. In *European Respiratory Review*. 2020.https://doi.org/10.1183/16000617.0038-2020
25. Wujtewicz, M. A., Dylczyk-Sommer, A., Aszkiełowicz, A., Zdanowski, S., Piwowarczyk, S., Owczuk, R. COVID-19 - what should anaethesiologists and intensivists know about it? In *Anaesthesiology Intensive Therapy*. 2020. https://doi.org/10.5114/AIT.2020.93756
26. Zheng, Z., Peng, F., Xu, B., Zhao, J., Liu, H., Peng, J., et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. In *Journal of Infection* (pp. e16–e25). 2020. https://doi.org/10.1016/j.jinf.2020.04.021
27. Shi, L., Wang, Y., Wang, Y., Duan, G., Yang, H. Dyspnea rather than a fever is a risk factor for predicting mortality in patients with COVID-19. In *Journal of Infection*. 2020. https://doi.org/10.1016/j.jinf.2020.05.013